Amendment to the Drawings

The attached sheets of drawings include changes to Figures 2 and 3. These sheets, which include Figures 2 and 3, replace the original sheets including Figures 2 and 3 and, in response to the Office's objection, are amended to replace the objected to letters and reproduce them in the required larger font.

Appendix 1: Replacement Sheets

Remarks/Arguments

The present application was filed with claims 1-25. Applicants elected with traverse, claims 1-18 and 21-25. Claims 19 and 20 have been withdrawn pending rejoinder. Claims 1, 2, 10, 17, 21, 23 and 25 are amended herein. No new matter has been added by way of these amendments. Applicants reserve the right to pursue the non-elected subject matter in one or more divisional applications.

Objections to the Specification

The Office has objected to the specification as reciting nucleotide sequences that have no sequence identifiers. The specification has now been amended to recite sequence identifiers for the unidentified sequences. In addition, an amended sequence listing, computer readable disc and statement under 37 CFR § 1.825 is attached hereto as Appendix 2. No new matter has been added by way of these amendments.

Objections to the Drawings

The Office has objected to Figure 2 (panel A) and Figure 3 as containing letters which are too small to read. Figures 2 and 3 have been amended herein to reproduce the objected to letters in a larger font.

Objections to the Claims

Claims 1, 2, 10, 17, 21, 23 and 25 are objected to because the claims recite the amino acid and nucleotide sequences using the term "SEQ ID NO.". the Office has suggested the use of the term "SEQ ID NO:". The claims have been amended herein to recite the suggested term. No new matter has been added by way of these amendments.

REJECTIONS TO THE CLAIMS

Claim Rejections Under 35 USC § 112, First Paragraph

Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph because, the Office finds that, while being enabled for a method of modifying a specific acyl-CoA such as 6-

CoA or 8-CoA as a substrate by formation of C-O bond, or a method of producing a specific macrotetralide (such as compounds 1-5) using a specific acyl-CoA such as 6-CoA or 8-CoA as a substrate etc. does not reasonably provide enablement for a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO:3 or 5 (read as fragments of SEQ ID NO:3 or 5); a polypeptide encoded by a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 1, 2 or 4; and a poly peptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4 and capable of C-O bond formation, wherein the biological molecule or the macrotetralide is not identified and the function of the fragment is not defined.

Applicants overcome this rejection in part and traverse this rejection in part. First, as amended herein claims 1, 2, 17, 21, 23 and 25 now recite that the polypeptide *consists* of the identified sequence. Thus, fragments of the identified SEQ ID NOs: are no longer encompassed by the claims. Further, the Office characterizes claims 1-18 and 21-25 as "directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO: 3 or 5; a polypeptide encoded by a nucleic acid comprising a nucleotide sequence of SEQ ID NO: 1, 2, or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4 and capable of C-O bond formation. The specification, however, only discloses cursory conclusions without data supporting the findings . . . because there are no indicia that the present application enables the full scope of the claims in view of the use of the sequences related to NonJ and NonK in the claimed methods as discussed in the stated rejection."

Specifically the Office cites to the factors identified in *In re Wands* wherein:

(1) The Office refers to the first of the *Wands* factors, the breadth of the claims finding the claims broad because they are thought to encompass: (i) unspecified variants regarding the polypeptides comprised by SEQ ID NO:3 or 5 (read as fragments); (ii) polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4 and capable of C-O bond formation; (iii) biological molecules as substrates being modified by

forming C-O bond; and (iv) macrotetralides or macrotetralide analogs to be produced, which are not adequately described or demonstrated in the specification.

In response to this aspect of the *Wands* factors, the rejection is overcome in part and traversed in part. Specifically, (i) the claims are amended herein (as discussed above) to recite that the claimed polypeptide "consists" of the amino acid sequence set forth in SEQ ID NOs: 3 and 5 (respectively) and are encoded by nucleic acid sequences consisting of those identified as SEQ ID NOs: 1, 2, or 4; (ii) the specification specifically identifies "stringent conditions" under which hybridization occurs at pages 17 and 18. Further, a discussion of the use of a mismatched primer that hybridizes to the native nucleotide for the generation of a mutant megasynthetase is given on page 53-54; (iii) in addition, the specification gives specific examples of the use of biological molecules as substrates being modified by forming C-O bond at, for example, the passages spanning page 49-65 (see, CREATION OF CHEMICAL DIVERSITY BY UTILIZING NonJK IN DIRECTED BIOSYNTHESIS) where the use of polypeptides nonJ or nonK are used to catalyze C-O bonds in a substrate. In addition, this passage describes tests and assays for the identification of products that are modified by the formation of C-O bonds, as recited in claim 10; further, the passage spanning pages 49-65 gives specific examples of the synthesis of macrotetralides and macrotetralide analogs that are produced by the invention and also describes methods for assaying for resultant products and the use of matrix-assisted laser desorption (MALDI) mass spectrometry (MS) analysis of the products and their identification. In addition, applicants point out that, as noted by the Examiner in the above quoted rejection, claims 1, 2, 10, 17, 21, 23 and 25 recite *methods* of modifying a biological molecule or producing a macrotetralide, or macrotetralide analogue in which the result of producing a C-O bond or a macrotetralide or macrotetralide analogue is the test which identifies the structure to function/activity relationship of the NonJ and NonK sequences and thereby by which the polypeptides and biological molecules are identified. Further, as pointed out above, the specification explicitly gives examples of the use of such polypeptides and biological molecules and further gives examples by which the tests verifying the structure to function/activity relationship is confirmed using specific assays to identify the formation of C-O bonds and macrotetralides or macrotetralide analogues. Therefore, the full scope of the claims does not encompass "sequences related" to NonJ and NonK but rather to the sequences identified in SEQ

ID NOs: 1-5 and further explicitly gives data and describes the use of the invention to modify biological molecules based on C-O bond formation. Therefore, this aspect of the rejection is overcome and should be withdrawn. Applicants respectfully request same.

(2) The Office then refers to the second *Wands* factor, the absence or presence of specific working examples. The applicants note that the Examiner has acknowledged that the specification has identified the C-O bond forming activity of NonJ and NonK in nonactin biosynthesis, that the NonJ and NonK sequences are set forth in SEQ ID NO: 3 and 5 respectively, that the nucleic acid sequences encoding NonJ and NonK are provided in SEQ ID NO: 2 and 4 respectively, that SEQ ID NO:1 sets forth a partial nucleic acid sequence of the nonactin biosynthesis gene cluster, that the use of NonJ and NonK as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8- CoA to produce specific macrotetralide compounds such as compounds 1-5. However, the Office states that, (i) the specification has not demonstrated the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides, (ii) has not identified any functional fragment of SEQ ID NO: 3 or 5, and (iii) any functional polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4.

These grounds for rejection are traversed in part and overcome in part. First, claims 1, 2, 10 17, 21, 23 and 25 recite a "*method*" wherein the method includes steps of "contacting biological molecules that are substrates for a polypeptide" identified thereby and wherein the polypeptide catalyzes C-O bond formation between the biological molecules as described above. Thus, the claims provide a test for the identification of biological molecules that can accommodate the formation of C-O bonds under the conditions recited. Second, claims 1, 2, 10, 17, 21, 23 and 25 are amended herein to recite that the specified sequences *consist* of the recited SEQ ID NOs. Third, the claims recite methods for the production of macrotetralides and macrotetralide analogues that use a polypeptide encoded by a nucleic acid that "specifically hybridizes under stringent conditions and *is capable* of C-O bond formation." In response, the specification explicitly describes hybridization strategies at page 17-18 and further, describes at for example, pages 49-65 (CREATION OF CHEMICAL DIVERSITY BY UTILIZING NonJK IN DIRECTED BIOSYNTHESIS) the use of the method to produce macrotetralides and their

analogues and assays for identifying the same. Thus, working examples of the use of the claims are explicitly recited in the specification. Thus, this aspect of the rejection is overcome and should be withdrawn.

(3) Next, the Office refers to the third of the *Wands* factors, the state of the prior art and relative skill of those in the art. Specifically, the Office refers to Walczak et al. as teaching the isolation and sequencing of 15559 bp of chromosomal DNA of the nonactin biosynthesis gene cluster and that two of the genes, NonK and NonJ that are unusual ketoacyl synthase (KAS)α and KASβ homologues. However, the Office states that general knowledge and level of the skill in the art do not supplement the omitted description, as the specification needs to (i) provide teachings on the use of various biological molecules as substrates; (ii) the identification of functional fragments; and (iii) related polypeptides of NonK and NonJ as well as the use of these peptides in the claimed method. However, this rejection is overcome in part and traversed in part due to (i) the teaching in the specification by examples teaching the use of biological molecules, such as 6-CoA and 8-CoA, as substrates and examples showing the efficacious use of substrates, such as the exemplary one identified and tests and assays identifying the formation of C-O bonds and their products. (ii) Functional fragments of the recited sequences are no longer encompassed by the claims and (iii) methods to isolate related molecules using standard techniques well-known in the art for isolation of related polypeptides by hybridization and examples of assays to determine functionality such as described, above, for part (2). Thus, this aspect of the rejection is overcome and should be withdrawn.

(4) Next, the Office refers to the fourth of the *Wands* factors, the predictability or unpredictability of the art. Specifically, the Office states that the use of various biological molecules as substrates and the identification of polypeptide sequence related NonK or NonJ are not adequately described in the specification, the invention is thought to be unpredictable regarding the sequences of functional peptides related to NonK or NonJ. As discussed for *Wands* factors three and four above, the claims recite *methods* whereby a biological molecule is contacted with a polypeptide consisting of the recited SEQ ID NO. Thus, the claims have been amended herein such that fragments of NonK or NonJ are not encompassed by the claims. Further, the methods provide function limitations and tests such that the biological molecules

must be amenable to the formation of C-O bonds catalyzed by NonJ and NonK. These functional limitations and tests are fully described in the specification at pages 49-65 (CREATION OF CHEMICAL DIVERSITY BY UTILIZING NonJK IN DIRECTED BIOSYNTHESIS). Thus, the rejection is overcome and should be withdrawn.

(5) The Office then refers to the fifth of the *Wands* factors, the amount of guidance presented and the quantity of experimentation necessary. In this aspect, the Office, again, states that the specification has not demonstrated; (i) the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides; (ii) has not identified any functional fragment of SEQ ID NO: 3 or 5; and (iii) any functional polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO 1, 2 or 4. Further, the Offices states there are no working examples demonstrating the use of various biological molecules as substrates and various polypeptide sequence related to NonK or NonJ in the claimed methods.

As discussed above, for *Wands* factors 2, 3 and 4, (i) the specification affirmatively discloses the use of various biological molecules as substrates, namely 6-CoA and 8-CoA that act as substrates for NonJ and NonK, as acknowledged by the Office. Further, the methods expressly recite the functional limitations that C-O bond formation occurs. The specification explicitly gives examples of experiments where the biological molecules is contacted with NonJ and NonK and further describes experiments performed using assays to confirm the formation of C-O bonds and identify the products of the identified reactions. Thus, the methods of the claims are fully disclosed and enabled by the specification and no significant experimentation other than the experiments and assays disclosed in the specification are needed to carry the use of biological molecules as substrates as the methods recited in the claims are fully supported; (i) in addition, as amended herein, claims 1, 2, 10, 17, 21, 23 and 25 do not encompass polypeptide related to NonK or NonJ, the rejection has been overcome and should be withdrawn; and (iii) with respect to functional peptides that specifically hybridize to SEQ ID NO 1, 2, or 4, the specification describes specific conditions needed to elicit specific hybridization of nucleotides. Further, as discussed above, the claims require the functional limitation that the nucleotides are then capable of catalyzing C-O bond formation. Finally, as discussed above, the specification gives specific

examples of experiments and assays used to confirm C-O bond formation and the use of MALDI-MS analyses that are used to confirm C-O bond formation and identify the product of the reaction. Thus, the specification provides explicit guidance on how to use the invention and there is no undue experimentation needed to use the invention. Thus, this aspect of the rejection is overcome and the rejection should be withdrawn.

(6) Finally, the Examiner refers to the last of the *Wands* factors, the nature of the invention, the Office states that the scope of the claim encompasses various biological molecules as substrates and various polypeptide sequences related to NonK or NonJ, but the specification does not provide sufficient teachings on the identities and use of these substrate and peptide variants in the claimed methods. As discussed above, the specification provides specific examples of the use of biological molecules as substrates. Moreover, the specification provides experiments and assays that can be used to test for the formation of C-O bonds in the substrate and further to identify the substrate and the products of the reactions. Further, as amended, the claims 1, 2, 10, 17, 21, 23 and 25 and those dependent therefrom, no longer encompass sequences related to NonK or NonJ. Thus, this rejection has been overcome and should be withdrawn.

Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Specifically, the Office states that claims 1-18 and 21-25 are directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO: 3 or 5 (read as fragment); a polypeptide encoded by a nucleic acid comprising nucleotide sequence of SEQ ID NO: 1, 2 or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2, or 4 and capable of C-O bond formation.

Specifically, the Office states that the specification (i) does not disclose a genus of variants of fragments of SEQ ID NO: 3 or 5; (ii) polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4 and capable of C-O

bond formation; (iii) biological molecules as substrates being modified by forming C-O bond; and (iv) macrotetralides or macrotetralides analogs in the claimed methods. Further the Office states that the specification has not identified any fragment of SEQ ID NO:3 and 5 that is functional and any functional poly peptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4. In addition, the Office states that the use of NonJ and NonK (SEQ ID NO: 3 and 5) as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds 1-5 (Fig. 11) does not provide a written description for a genus of various biological molecules as substrates and various macrotetralides to be produced in the claimed method. The Office states that without guidance on structure to function/activity for fragments of SEQ ID NO: 3 or 5 and polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 1, 2 or 4 one skilled in the art would not know how to identify a functional polypeptide. The Office states that the specification lacks description on structure to function/activity relationship of NonJ and NonK variant sequences, and the use of these sequences to modify various biological molecules to produce various macrotetralides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in full.

Applicants traverse this rejection in part and overcome this rejection in part. First, claims 1, 2, 10, 17, 21, 23 and 25 have been amended to so as not to encompass any fragments of the recited sequences. Thus, the specification does not encompass a genus of variants of fragments of SEQ ID NO: 3 or 5. Second, the specification explicitly recites conditions and methods for hybridizing nucleotides at pages 17-18 and describes experiments for catalyzing C-O formation and methods for assaying for such. Third, the specification gives examples of biological molecules used as substrates, namely 6-CoA and 8-CoA and methods for identifying the efficacy of the molecule as a substrate capable or being modified by C-O bond formation (see, for example, CREATION OF CHEMICAL DIVERSITY BY UTILIZING NonJK IN DIRECTED BIOSYNTHESIS at pages 49-65). Fourth, the specification does disclose the use of the invention to produce macrotetralides, as acknowledged by the Office, such as compounds 1-5 shown in Fig 1 and in Table 1 on page 64 of the specification. Thus, the invention is fully described in the specification providing a description of the use of the elements recited in the

claims, describing the use of experiments and assays to test for the functional limitations set forth in the claims and describing and teaching analyses and assays useful for identifying the products of the reactions recited in the claims. Therefore, the rejection is overcome and should be withdrawn.

Claim Rejections - 35 USC §112, Second Paragraph

Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. Specifically, the Office states that claims 1-18 and 21-25 are indefinite because the claim recites the term "a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO: 2 (or SEQ ID NO: 4)" or "a nucleic acid hybridizing under stringent conditions thereto". This rejection is traversed in part and overcome in part. Specifically, claims 1, 2, 10, 17, 21, 23 and 25 have now been amended to specifically recite that the conditions of hybridization are very stringent conditions as explicitly defined o page 18 of the specification. Further, the specification explicitly defines various conditions of stringency and wash conditions at, for example, pages 17-18. Therefore, the rejection is overcome and should be withdrawn.

Claims 17, 18 and 25 are found to be indefinite because the claim recites the term "(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO: 3 or 5". The rejection is overcome as claims 17 and 25 are amended herein to recite "(a) a polypeptide polypeptide ~~encoded by~~ consisting of an amino acid sequence set forth in SEQ ID NO: 3 or 5". Thus, the rejection is overcome and should be withdrawn.

CONCLUSIONS

In view of the amendments and arguments presented herein, applicants submit that the application is now in order for allowance. Early notification of such action is earnestly solicited. Applicant requests that the Examiner telephone the undersigned in the event a telephone discussion would be helpful in advancing the prosecution of the present application. The Director is authorized to charge any additional fees or underpayment of fees regarding this response, including extensions for reply, to Deposit Account 07-1509.

Respectfully submitted,

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